TUMORS OF THE THYROID*

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THYROID tumors have been of constant interest because of the difficulty of diagnosis of certain types; now the possibility has been raised that radioactive iodine may offer a useful therapeutic tool.

Most enlargements of the thyroid are not tumors. Enlargement of the gland, either diffuse or nodular, is much more frequently due to metabolic disorders than to neoplasia. Until recent years, there has been much confusion between the true adenomas of the thyroid and the nodular hyperplasias, and still some room for argument exists.

I have found the following criteria for adenoma of the thyroid to be helpful in differentiating this lesion from thyroid nodules of non-neoplastic origin. First, an adenoma should represent a single homogeneous type of tissue. Second, it should be definitely encapsulated. Third, it should compress surrounding thyroid tissue. Usually, it differs sharply in histology from the surrounding tissue. In some of the nodular goiters, even these criteria may prove unsatisfactory and uncertainty may exist as to type of lesion with which we are dealing.

The origin of thyroid adenomas is as uncertain as the origin of adenomas in other organs. In our laboratory five types of adenoma are recognized: the embryonal adenoma, in which masses and strands of poorly differentiated thyroid cells traverse a rather gelatinous stroma; the fetal adenoma, in which poorly developed follicles occur, usually embedded in a rather abundant gelatinous stroma; the simple adenoma which may closely resemble the histologic picture of the normal thyroid gland; the colloid adenoma, in which extensive storage of colloid occurs, and the follicles are greatly distended; the Hürthle cell type of adenoma, characterized by large polyhedral cells with rather strikingly clear cytoplasm.

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The so-called toxic adenoma is quite frequently diagnosed but very rarely occurs. Usually, when this term is applied, it is used to describe a nodular goiter with associated hyperthyroidism. Hyperfunction of the cells of an adenoma is one of the rarest changes encountered.

The adenomas are also of special interest because of the borderline position which they occupy between the benign tumors on the one hand and the malignant tumors on the other. There is a group of thyroid adenomas, usually indistinguishable from other adenomas grossly, which give rise to metastasis. The metastases may faithfully reproduce the parent adenoma or they may be even more differentiated resembling well-formed adult thyroid tissue, the so-called benign metastasizing goiter. The only clue to the malignancy of these tumors may be invasion of one or more veins by the neoplastic tissue. Sometimes this is grossly obvious with a solid cord of tumor filling one of the major thyroid veins or even the jugular vein. More often it is relatively inconspicuous and only microscopic examination will reveal its presence. This vascular invasion may or may not be accompanied by some invasion of the capsule. Not every case that shows microscopic evidence of blood vessel invasion develops metastases. Indeed, the frequency is under 10 per cent. It is likely that a relatively extensive amount of vascular invasion occurs before metastases become established, since the proportion of tissue removed for histologic examination is relatively small. Interestingly enough, I have seen only one case in which we did not find blood vessel invasion and in which metastases subsequently developed.

As would be expected from the high degree of differentiation of these tumors, their clinical course is relatively slow. Metastases occur most frequently in bone. In one case I recall, the patient lived seven years after the metastases were discovered. Likewise, a long latent period may pass between the development of the primary tumor and the appearance of metastases.

The commonest of the adenomas to show blood vessel invasion, as would be expected from their growth potentialities, are the embryonal and the fetal adenomas. In checking for the occurrence of blood vessel invasion, it is important not to be misled by artefacts. In the course of preparation of the sections, it is quite possible that portions of the tumor may be dislodged and caught in the blood vascular spaces. Consequently, I always like to see actual invasion of the wall of the vessel by the

tumor or adherence of the tumor tissue to the wall.

As was so clearly pointed out by Graham, the propensity to invade blood vessels is quite striking in all types of thyroid malignant tumors, regardless of their degree of differentiation, and is consequently a very valuable criterion of malignancy.

There has been a good deal of controversy concerning the papilliferous tumors. These may arise from the thyroid proper or from lateral aberrant thyroid tissue. The five types described by Moritz and Bayless are useful in considering this group: (1) The papilliferous cystadenoma, a benign tumor which represents hyperplasia of the lining epithelium of a cystic adenoma; (2) the papilliferous adenoma, which represents epithelial proliferation of an hyperplastic type within the follicles of a pre-existing adenoma, and is non-malignant; (3) the papilliferous carcinoid, which represents focal papillary hyperplasia, is non-encapsulated and occurs in a non-neoplastic thyroid gland; (4) the papilliferous adenocarcinoma arising from malignant change in a papilliferous cystadenoma, which shows capsular invasion or metastasis to regional lymph nodes; and (5) the papilliferous malignant adenoma, which shows a papillary intra-acinar hyperplasia in an adenoma with malignant characteristics, i.e., blood vessel invasion, capsular invasion, and sometimes metastasis to regional lymph nodes.

It has been our custom to differentiate three types of true papillary tumors: The benign papillary cystadenomas which may originate either within the thyroid or in lateral aberrant thyroid tissue, which are not clinically dangerous; the malignant papillary adenocystomas which seem to have the same origin as the foregoing but which, because of a greater growth potential, may metastasize chiefly to regional lymph nodes or lungs, invade blood vessels, and invade local tissues; the papillary adenocarcinoma which will be mentioned further later.

Even in those papillary cystadenomas that are malignant, the clinical course tends to be relatively slow, and fortunately, the results obtained with surgery combined with roentgen radiation are fairly satisfactory. Two-thirds of all patients treated were surviving at the end of five years.

When one finds a papillary tumor of thyroid origin in the neck, the problem always arises as to whether or not the thyroid should be removed either wholly or in part. If the thyroid is normal on palpation, there is no reason for operative interference, and it may safely be assumed that the tumor is of lateral aberrant origin. If, however, there is

enlargement or irregularity of the thyroid, at least a hemi-thyroidectomy including the abnormal tissue is indicated.

In the group of thyroid tumors of moderate malignancy we include the adenocarcinomas. These may be papillary, of alveolar type or of Hürthle cell type. They often give indication of origin from pre-existing adenomas, although not infrequently the development of the tumor has destroyed all evidence of the initial focus and the existence of a pre-existing adenoma may be deduced only from the history given by the patient.

The first subgroup of adenocarcinomas is the papillary form. This frequently invades the thyroid gland and adjacent normal tissue. The epithelium is variable in size and shape, usually with fairly well-defined cell borders. The epithelium tends to heap up rather than to form a single well-defined layer as is the case in the papillary cystadenoma. Occasionally, follicles and colloid may be present in the tumor. About 80 per cent of the patients bearing these tumors survive five years.

The alveolar type of adenocarcinoma is less differentiated and is made up of masses and strands of epithelial cells. The stroma is variable in amount. Here and there definite follicles are formed. These rarely may contain colloid. In this group only 27 per cent survived five years.

The rarest of the adenocarcinomas is the Hürthle cell type, which resembles closely the Hürthle cell adenoma already described, with large, clear acidophilic cells, but the arrangement is irregular, and invasion of adjacent thyroid tissue occurs. Mitoses, while not abundant, occur occasionally. The highly malignant carcinomas of Group 3 vary widely in appearance. The undifferentiated carcinoma simplex or small cell carcinoma occurs in two distinct forms; the compact form is readily recognizab'e by its masses of anaplastic epithelial cells without formation of follicles or of lumina. There is usually a high degree of mitotic activity. The diffuse type is much more difficult to recognize and is frequently confused with lymphoma or even chronic thyroiditis. The cells of the tumor are widely scattered. They are small with scanty cytoplasm and a rather small pyknotic nucleus. The stroma is rather dense, and the cells of the tumor are irregularly scattered through it, replacing much of the normal thyroid structure and extending out into the surrounding tissues. To render the picture more confusing, there may be scattered lymphocytes and macrophages present in the stroma as well. Fortunately, there are usually some small clusters of the cells

arranged in characteristic epithelial pattern. In this group only 22 per cent survived.

The giant cell carcinoma, sometimes called carcinosarcoma, is the most striking of the thyroid malignant tumors. Its large, bizarre cells and irregular mitoses make it easily recognized upon microscopic examination. It tends to occur in women about 50 or 60 years of age. It is very rapidly growing, extending widely and not infrequently compressing the trachea. The texture of the tumor is soft and meaty, rather more suggestive of a sarcoma than of a carcinoma.

In addition to these more frequent carcinomas of the thyroid, there are three malignant tumors which occur there very rarely. First, the true fibrosarcoma which may be recognized by the fact that its cells form fibroglia and collagen fibrils. Second, epidermoid carcinomas occasionally develop, either from epithelial nests or by metaplasia of thyroid epithelium. The third type is a true lymphoma of the thyroid, which must be differentiated from both the struma lymphomatosum of Hashimoto and the carcinoma simplex of diffuse type. Its appearance and behavior is comparable to that of lymphomas occurring elsewhere.